Remarks

Upon entry of this Amendment, claims 20-25, 27-30, 32-39 and 42-58 will be pending. Applicants have amended claims 20 and 27, currently on file, to more clearly define the scope of protection being sought. Support for the amendment can be found throughout the specification as filed, for example, at page 12, lines 22-27, and in the Examples. In this regard, Applicants also make reference to MPEP Section 2173.05(i), which indicates that any alternative element positively recited in the specification may be excluded in the claims.

Applicants have also added new claims 55 to 58 in order to claim additional embodiments of the invention. Support for the new claims can be found throughout the application as originally filed, for example, at page 12, lines 22-27; page 14, lines 2-6; page 15, line 22 to page 16, line 10; page 20, lines 12-14; page 22, lines 25-26; and at claim 19 as originally filed.

35 U.S.C. 112

Applicants acknowledge with thanks the Examiner's withdrawal of the former rejections of claim 20 under 35 U.S.C. 112, second paragraph, and of claims 20-25, 27-30, 32-39, 42 and 43 under 35 U.S.C. 112, first paragraph.

35 U.S.C. 102

The Examiner has rejected claims 20-24, 25, 27-30, 32-35, 38, 39 and 42-54, under 35 U.S.C. 102(b), alleging that the claims are anticipated by Lee-Shanok (Construction and preliminary characterisation of papaya mosaic virus as an expression vector for the presentation of foreign epitopes, Thesis for Degree of Master of Science, University of Toronto, 1999). Specifically, the Examiner alleged that Lee-Shanok discloses a method of potentiating an immune response against antigenic epitopes, specifically HCV epitopes recombinantly engineered to be expressed by papaya mosaic virus particles. The Examiner has further alleged that Lee-Shanok discloses oral administration of the papaya mosaic virus particles fused with the HCV epitope. While the Examiner has acknowledged that Lee-Shanok does not specify what kind of immune responses could be generated due to the administration of papaya mosaic virus particles fused with the HCV nucleocapsid, the Examiner has alleged that because Lee-Shanok discloses that papaya mosaic virus particles fused with the HCV nucleocapsid gene can be used as a vaccine and

broadly refers to immune responses, it is expected that humoral and cellular responses are generated by the method disclosed by Lee-Shanok.

Applicants respectfully traverse the Examiner's rejection for the following reasons. Independent claims 20 and 48, currently on file, are directed to methods of potentiating an immune response in an animal, comprising administering to an animal an antigen and an effective amount of an adjuvant. The recited adjuvant is either a papaya mosaic virus (PapMV), or a virus-like particle (VLP) comprising PapMV coat protein or modified PapMV coat protein (claim 20), or a virus-like particle (VLP) comprising modified PapMV coat protein having the antigen fused to the C-terminus of the modified PapMV coat protein (claim 48). Both claim 20 and claim 48 specifically recite that the PapMV coat protein or modified PapMV coat protein is capable of multimerization to form the VLP.

Lee-Shanok describes the engineering of clones comprising recombinant papaya mosaic virus (PapMV) fusion proteins. The clones initially developed by Lee-Shanok were N-terminal replacement clones in which 18 amino acids of the N-terminus of the PapMV coat protein (CP) were deleted and replaced with a sequence from hepatitis C virus (HCV). These N-terminal replacement clones, however, demonstrated very low infectivity in *Chenopodium amaranticolor* and were incapable of infecting papaya plants (the PapMV systemic host). As noted in Lee-Shanok, this is likely due to the failure of the resulting viral particle to assemble, *i.e.* multimerise (see Lee-Shanok, results for p 12, page 83, lines 1-7). As a result, a clone comprising two species of CP, a wild-type CP and a CP-fusion, resulting in viral particles having a mosaic of CPs (see Lee-Shanok, page 58, line 14), had to be developed in order to obtain an infectious viral particle. In this latter case, the duplicate CP system was designed in order to express larger epitopes based on the premise that a capsid fusion protein would be unable to assemble (due to the steric hindrance constraints of particle assembly imposed by the foreign inserts), unless a free wild-type capsid protein was present along with the fusion protein (see Lee-Shanok, page 32, lines 10-19; page 83, lines 7-10; and page 87, lines 1-9). In fact, the author emphasizes that until the duplicate protein system was developed, only PapMV capsid fusion proteins carrying short foreign epitopes, *i.e.* a maximum of 11 amino acids, at the N-terminus had been successfully expressed in host plants (see Lee-Shanok at page 82, lines 15-20).

Furthermore, while Lee-Shanok *speculates* that the disclosed recombinant PapMV proteins can be used as vaccines, the reference fails to provide evidence that the described PapMV clones would actually result in an immune response in an animal. Moreover, nothing in Lee-Shanok even suggests that PapMV or a PapMV VLP could be used as an adjuvant to potentiate an immune response, as recited in the currently pending claims. The main objective of the cited art is to modify a PapMV protein to form a carrier protein (see Lee-Shanok, at page 1, lines 8-10, and page 22, lines 1-22) that can be expressed in plants. Even where speculative discussion of eliciting an immune response in mammals is provided, the author indicates that the expression system would merely act as a vehicle for the presentation of an epitope to the immune system of a mammal (Lee-Shanok, page 22, lines 8-11). As such, the Applicants assert that the only method disclosed by Lee-Shanok is a method of preparing infectious viral particles containing recombinant duplicate CPs for inoculating plants. In contrast, the instant specification provides numerous examples demonstrating that PapMV itself (see Example II), as well as PapMV VLPs administered together with an antigen (see Example II, and Figure 7) or fused to an antigen (see Example III, and Figure 8), are capable of eliciting a long-lasting immune effect in mice. In addition, the Examples provided in the present application indicate that the immune response to an antigen is increased (*i.e.* potentiated) when the antigen is administered with PapMV (see, for example, Figure 7).

Furthermore, as noted above and described at page 30, lines 20-21, of Lee-Shanok, the objective of the research described in this thesis was to modify the PapMV expression system so that the engineered PapMV clone would be able to replicate in plants. As described in Lee-Shanok, the C-terminus of PapMV was known in the art to be required for infectivity (see Lee-Shanok at page 27, lines 4-5) and mutations in this region or in regions of the CP other than the N-terminus, or addition of non-viral nucleotides at the 3'-end of PapMV transcripts, had been shown to significantly decrease or abolish infectivity (see Lee-Shanok at page 26, line 10 to page 27, line 1). As such, Lee-Shanok describes engineered PapMV with fusions at the N-terminus of the CP *only*. In this regard, Applicants respectfully direct the Examiner's attention to the language of pending claims 44 and 48, which specifically recite that the antigen is fused to the C-terminus of the PapMV coat protein.

Given the foregoing, Applicants assert that Lee-Shanok does not describe each and every element of the invention as recited in independent claims 20 and 48 and, as such, fails to anticipate the claimed invention. Applicants have, however, without conceding to the correctness of the Examiner's rejections, but for the purpose of expediting examination, amended claim 20, to recite that the antigen is either not linked to the PapMV or VLP, or is fused or covalently attached to a coat protein of the PapMV, or to the PapMV coat protein or modified PapMV coat protein, at a location other than the N-terminus, such that the antigen is disposed on the outer surface of the PapMV or VLP.

As noted above, Lee-Shanok does not disclose a method of using PapMV as an adjuvant, nor does Lee-Shanok disclose or teach a recombinant papaya mosaic virus (PapMV) CP having an antigen fused or otherwise attached at a location other than at the N-terminus of the CP. Moreover, as noted in Lee-Shanok, it was generally accepted in the art prior to the filing date of the instant application, that in order for an antigen to be expressed on the exterior of a potexvirus viral particle where it will be easily recognized by an immune system, the foreign insert must be inserted into the N-terminus of the potexvirus (see Lee-Shanok, page 22, lines 8-11; and page 86, lines 11-14). As such, Applicant asserts that the disclosure of Lee-Shanok actually teaches away from the subject matter of claims 20 and 48, submitted herewith, as it discourages the construction of a recombinant PapMV or PapMV VLP having an antigen fused or attached at a location other than at the N-terminus of the capsid protein.

For the reasons set forth above, Applicants assert that the subject matter of the claims submitted herewith is novel over the prior art and, therefore, comply with 35 U.S.C. 102(b). Accordingly, Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. 103

The Examiner has rejected claims 36 and 37, under 35 U.S.C. 103(a), alleging that the claims are unpatentable as being obvious in light of Lee-Shanok (noted above) and the common general knowledge in the art of vaccine development. Specifically, the Examiner alleged that while Lee-Shanok does not teach the particular immunization schedule currently claimed, it would have been well within the knowledge and ability of the ordinary artisan to implement various immunization schedules including changing the order of antigen versus adjuvant being

administered. The Examiner further alleged that one of ordinary skill would have been motivated to administer an adjuvant prior to administration of an antigen and vice-versa for the purpose of optimizing the immunization effect.

Applicants respectfully traverse the Examiner's rejection. For the reasons outlined above, Applicants assert that the subject matter of independent claim 20, currently on file, is both novel and inventive over Lee-Shanok. Applicants assert that the subject matter of dependent claims 36 and 37, is thus likewise inventive over Lee-Shanok. Solely in order to expedite prosecution of the instant application, however, Applicants have amended claim 20, from which claims 36 and 37 depend, as noted above. Applicants submit that dependent claims 36 and 37 comply with 35 U.S.C. 103(a), as the subject matter of these claims is inventive over the cited art. Applicants, therefore, respectfully request that this rejection be withdrawn.

Conclusion

Applicants submit that all of the stated grounds for rejection have been properly traversed, accommodated or rendered moot. Applicants, therefore, respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided. Prompt and favourable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,
JUNEAU PARTNERS, PLLC

Todd L. Juneau Reg. No. 40,669
JUNEAU PARTNERS, PLLC Customer No. 50438
2121 Eisenhower Avenue, Suite 200
Alexandria, VA 22314
Tel: (703) 548-3569